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(54) Title: IMPROVED PHARMACEUTICAL COMPOSITION CONTAINING A PPAR ALPHA AGENT AND A PROCESS FOR PREPARING IT

(57) Abstract: Oral semi-solid or liquid composition for treating hyperlipidemia or hypercholesterolemia in humans, which comprises at least an effective amount of a peroxisome proliferator activated receptor alpha agent (PPARα), one polyglycolized glyceride and one hydrophilic disintegrating agent.

Improved pharmaceutical composition containing a PPAR alpha agent and a process for preparing it

ABSTRACT

An oral semi-solid composition containing at least one peroxisome proliferator activated alpha agent (PPARα) at a therapeutical dose, a polyglycolized glyceride and an hydrophilic disintegrating agent.

BACKGROUND OF THE INVENTION

Fibrates are old hypolipidemic drugs with pleitropic effects on lipid metabolism. Their intimate molecular mechanisms of action have been mysterious for a long time. Recently, it has been shown that the pharmacological effect of fibrates depends on their binding to "Peroxisome Proliferator Activated Receptor alpha" (PPAR alpha). The binding of fibrates to PPAR induces the activation of the inhibition of multiple genes involved in lipid metabolism through the binding of the activated PPAR alpha to "Peroxisome Proliferator Response Element" (PPRE) located in the gene promoters. Furthermore, it was recently demonstrated that fibrates are potent antiinflammatory molecules through an indirect modulation of the nuclear-factor-Kappa B activity.

Fenofibrate or P-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. Initially, the usual daily dosage was 300 mg which was administered in two or three doses. A few years later, a suprabioavailable composition of fenofibrate was developed and marketed by Laboratoires Fournier, France (EP 0030532). 200 mg of fenofibrate from this composition was bioequivalent to 300 mg of the initial composition. Fenofibrate is absorbed as fenofibric acid which is responsible

for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Fenofibrate is presently available in a pharmaceutical dosage form consisting of hard gelatin capsules containing fenofibrate, lactose starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is effectively absorbed and found in the blood as fenofibric acid, the main metabolite responsible for pharmacological activity.

The first attempt to improve the bioavailability of fenofibrate was performed by Ben-Armor et al, by solubilizing the fenofibrate in dimethyl isosorbide, a nonaqueous solvent with a miscible wetting agent (Labrafil M1944CS) with HLB of between 3-4. In order to use the product in capsules, colloidal silicon oxide was added to increase the viscosity. The liquid so obtained was placed in hard gelatin capsules which, to be leak proof, were sealed. In vivo studies with this formulation indicate that there was no statistically significant difference in bioavailability between this liquid formulation and the conventional form when the product was given with food.

European Patent Application 0330532 discloses a fenofibrate composition wherein the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl sulfate is described as the solid wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipient such as lactose, starch, polyvinyl pyrollidone and magnesium stearate. A formulation of this composition is actually available on the French market under the trade name Lypanthyl® 200, Fournier, France. A study comparing this formulation (Lypanthyl® 200) to the conventional form was undertaken and a statistically significant increase in bioavailability was indicated for the

former. In particular, it was found that 67 mg of the new form gives the same amount absorbed as does 100 mg of the conventional form.

Unfortunately, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, is a time consuming and costly operation. Further, an inherent drawback of micronization is that the material obtained must comply with very stringent particle size specifications. Indeed, the solubility and thus bioavailability depend on the particle size, whereby the presence of only some larger fenofibrate particles in a dosage form containing 160mg could modify greatly the solubility and bioavailability.

The Canadian patent 2,214,895 describes an improved formulation of fenofibrate obtained by making a solid dispersion of fenofibrate and a disintegrating agent.

Moreover, the filling of hard gelatin capsules with a micronized powder is a difficult operation, particularly if weight variation homogeneity is considered.

Hence, a need exists for a fenofibrate formulation that avoids the use of co-micronization, while providing a bioavailability comparable to that afforded by the conventional fenofibrate formulation which uses co-micronization.

Consequently, there was a need to dispose of a fenofibrate composition easy to manufacture and providing a high bioavailability after oral intake. Such a composition is disclosed in US patent 5,545,628 based on a semi-solid formulation containing fenofibrate and an excipient containing one or more polyglycolized glycerides.

Nevertheless, after that, the US patent 6,277,405 describes a composition of fenofibrate allowing to still improve the bioavailability of fenofibrate after oral intake. This patent describes the use of:

a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate active ingredient in a micronized form having a size smaller than 20 microns (µm), a hydrophilic polymer and, optionally, a surfactant, said hydrophilic polymer making up at least 20% by weight of an (a) and :
b) optionally one or several outer phase(s) or layer(s).

The composition described in the US patent 6,277,405 allows indeed to improve the bioavailability of fenofibrate in comparison with the commercial forms available on the market for several years (TRICOR® 200, LIPIDIL® 200, LIPANTHYL® 200, Fournier, France) and corresponding to the older US patent EP 0330532.

Pharmacokinetic studies have demonstrated that 200 mg of the commercial formulation are equivalent to 160 mg of the composition corresponding to the patent 6,277,405 (i.e. a 20% increase of bioavailability), which is already commercialized in several countries (LIPIDIL® 160, LIPANTHYL® 160).

Nevertheless, the process and the composition described in the patent 6,277,405 are complex, difficult and long to manufacture, and expensive. There was therefore still a need for a fenofibrate oral composition allowing to reach a similar bioavailability as that of US patent 6,277,405 but with a simpler and cheaper manufacturing process. The formulation described in US patent 5,545,628 did not offer a sufficient bioavailability. Indeed, this kind of composition gives a bioavailability similar to that of Tricor® 200 mg but 20% inferior to the LIPIDIL® 160 mg.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a PPARα agent containing composition (preferably a fenofibrate containing composition) with a very high bioavailability, which can be prepared without requiring micronisation and/or the presence of an hydrophilic polymer and/or the necessity of an outer phase layer. It is also an object of the invention to describe an easy, reliable and cheap process for manufacturing the new composition.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Oral semi-solid pharmaceutical compositions present various advantages:

The advantages of the semi-solid formulations are multiple for a PPAR derivative: protection of the active ingredient from air and humidity, possibility of increasing the dissolution rate of the molecule and hence of bioavailability, diminution of the risk of contamination of the operator, diminution of the risk of cross contamination, no possibility of demixing under the effect of vibrational mixing during manufacturing process, facility of the production process. The choice of the nature of the formulation of course influenced the stability of the pharmaceutical form and the bioavailability of the drug contained in it. Generally, a maximum bioavailability is achieved by preparing and keeping the drug in the amorphous/solubilized state in a solid dispersion or in a lipid-based formulation. For these systems, the barrier we are avoiding is the compound « washing-out » of solution to a large extent into a insoluble crystalline form during the dissolution/release step in vivo.

The use of polyglycolized glycerides in this kind of semi-solid compositions has already been described in US patent 5,545,628, the content of which is incorporated to the present specification by reference.

It has now been observed that by using simultaneously a polyglycolized glyceride and a disintegrating agent in a semi-solid or liquid fenofibrate composition, it was possible reach the bioavailability and the mean plasma concentration of the commercial Lipidil ® formulation, the latter formulation requiring a co-micronization step as taught in EP 0330532.

The present invention provides a pharmaceutical formulation for treating hyperlipidemia and/or hypercholesterolemia in a mammal, which contains an effective amount of a PPARα agent or a mixture of PPARα agents, advantageously fenofibrate, an excipient which contains one or more polyglycolyzed glycerides, the polyglycolyzed glycerides preferably having an HLB value of at least about 10, and one disintegrating agent.

PPAR agents are agents having a "peroxisome proliferation activated receptor activating effect", i.e. agents activating the binding of PPAR to peroxisome proliferator response element (PPRE), as well as agents activating the PPAR for its binding to PPRE.The agent as such, or a metabolite thereof , or a compound generated by the organism due to the presence of the agent is bound to the PPAR, whereby inducing the binding of PPAR to PPRE.

PPAR agents (alpha, delta and/or gamma) are agents for which the data determined by measuring the receptor-activating effect of a certain compound are statistically judged as being significantly different from the control data determined in the absence of the compound. Many documents disclose PPAR agents. For example, reference can be made to US 6,365,586;US 6,331,627 ; US 6,214,820, etc. disclosing or referring to such agents.

In the composition of the invention, the PPAR agent is advantageously an agent with a low water solubility, such as a water solubility similar or smaller

to the water solubility of fenofibrate (for example a water solubility expressed in g/l corresponding to less than 5 (preferably less than 2) times the solubility of fenofibrate in water (pH 7, temperature 20°C).

The PPAR agent is more precisely a PPARα agent, such as a compound of the fibrate family, such as fenofibrate, ciprofibrate, Clofibrate, Gemfibrozil, Bezafibrate or combinations thereof, fenofibrate and combinations containing fenofibrate being most preferred.

The present invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is at least partially soluble, whereby particle size specifications are not required.

Advantageously, the present invention also relates to the addition of a suspension stabilizer to the molten solution of PPARα (such as fenofibrate)-polyglycolyzed glycerides. The suspension stabilizer avoids the formation of PPARα crystals, such as fenofibrate crystals, during the cooling of the filled hard gelatin capsules. Suitable suspension stabilizers which may be used are, for example, cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, and hydroxyethylcellulose, povidone, poloxamers, .alpha., .OMEGA.-hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene)bloc polymers. Other suspension stabilizers equivalent to these stabiliers may, of course, also be used.

The present invention is also particularly advantageous for the production of a pharmaceutical composition in that the hot, homogeneous PPARα (such as fenofibrate) solution is filled in hard gelatin capsules. This filling process permits to ensure a very precise PPARα (such as fenofibrate) amounts in each capsule.

The present invention is particularly advantageous as well for the production of the present pharmaceutical composition in that the process for manufacturing the composition requires very few steps such as melting, mixing and filling. This renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders.

Polyglycolyzed glycerides which may be used in the present invention are generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters of polyethylene glycols with a mean relative molecular mass between about 200 and 6000. They may be obtained by partial transesterification of triglycerides with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids using known reactions. Preferably, the fatty acid component contains 8-22 carbon atoms, particularly 10-18 carbon atoms. Examples of natural vegetable oils which may be used include palm kernel oil and palm oil. However, these are only examples. The polyol suitably has a molecular weight in the range of about 200-6000 and preferably contains polyethylene glycol, although other polyols may be employed, such as polyglycerols or sorbitol. They are available on the market under the trade name Gelucire® (Gattefossé, France).

As noted above, the HLB of the polyglycolized glycerides is preferably at least about 10, and more preferably between about 12 and 15. The melting point of the polyglycolized glycerides may be between about 18.degree. C. and 60.degree. C. However, it is especially desirable to use polyglycolized glycerides having a melting point above 30.degree. C., and preferably above 35.degree. C., since there is no need for sealing the capsule, to assure the leak proofness thereof, when such excipients are used.

Further, two or more polyglycolized glycerides may be mixed in order to adjust both the HLB value and the melting point to a desired value. The

HLB value and melting point of the composition may further be adjusted with the addition of components such as polyethylene glycols, polyoxyethylene glycols fatty acid esters, and fatty acid alcohols. In view of the present specification, it is well within the skill of the artisan to mix the polyglycolized glycerides to obtain desired HLB values and melting points.

Although the present invention is not bind by any particular theories, one plausible mechanism of operation for the present invention is that upon cooling, the melted mixture of hot PPARα (such as fenofibrate)-polyglycolized glycerides maintains the PPARα (such as fenofibrate) in liquid form. When absorbed in the gastrointestinal tract of a patient, the gastrointestinal fluids are able to dissolve the PPARα (such as fenofibrate) due to the HLB value of the excipient mixture, whereby PPARα (such as fenofibrate) is readily absorbed.

The release of the drug from this kind of semi-solid lipophilic matrix is operated by a phenomenon of erosion-diffusion of the form when it is in contact with the gastro-intestinal fluids. As most excipients have relatively lipophilic properties, the release of the drug from the composition is relatively slow.

It was consequently a goal of the present invention to increase the release of PPARα (such as fenofibrate) from this kind of composition.

Surprisingly enough, this increase of release has been obtained by adding in the formulation very hydrophilic excipients (disintegrating agents) not soluble in the fatty mass. Such hydrophilic excipients may be the following ones but are not restricted to them: sodium starch glycolate, sodium croscarmellose, crospovidone, pregelatinized starch, maize starch, Aerosil® (colloidal silicone dioxide).

These kinds of hydrophilic substances while not soluble are able to be dispersed homogeneously in the fatty mass and remain homogeneously dispersed after capsule filling and cooling.

The invention relates also to method for treating or preventing hyperlipidemia or hypercholesterolemia in a patient, in which at least an effective amount of a peroxisome proliferator activated receptor agent is orally administered to the patient simultaneously with at least one polyglycolized glyceride and one hydrophilic disintegrating agent. In this method, the PPAR agent, the polyglycolized glyceride and the disintegrating agent are preferably of the type disclosed for the composition of the invention.

The invention further relates to a process for the preparation of an oral semi-solid or liquid composition containing at least an effective amount of PPAR agent, at least one polyglycolised glyceride and one hydrophilic disintegrating agent, in which the PPAR agent in powder form and hydrophilic disintegrating agent are mixed to a molten mixture containing at least one polyglycolised glyceride.
Advantageously, the PPAR agent and the hydrophilic disintegrating agent are mixed successively with the molten mixture.
Preferably, the PPAR agent is first mixed with the molten mixture, and before adding the hydrophilic disintegrating agent, the homogeneous dispersion of the PPAR powder in the molten mixture is controlled

The weight ratio polyglycolized glyceride(s)/hydrophilic disintegrating agent in the composition of the invention or in the method of the invention or in the process of the invention is for example comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, for example between 8 and 25.

The weight ratio PPAR agent/hydrophilic disintegrating agent in the composition of the invention or in the method of the invention or in the process of the invention is for example comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, for example between 6 and 25.

The weight ratio PPAR agent/polyglycolized glyceride(s) in the composition of the invention and in the method of the invention or in the process of the invention is for example comprised between 10 and 0.1, advantageously between 5 and 0.5, preferably greater than 1, such as between 1.1 and 2, for example 1.2, 1.5, etc.

BRIEF DESCIPTION OF THE DRAWINGS

Figure 1 is a graph showing the in vitro comparative dissolution profiles of 2 semi-solid formulations of fenofibrate with and without disintegrant

Figure 2 is a graph showing the in vitro comparative dissolution profiles of 2 semi-solid fenofibrate compositions containing different disintegrating agents

Figure 3 is a graph showing the pharmacokinetic results of comparative study in 18 volunteers for fenofibrate (log-transformed data).

EXAMPLES

An example of preferred manufacturing process is given hereinbelow:

The manufacturing process allowing to obtain the composition described in the present invention is, for example, as given hereinbelow. In this example, fenofibrate is used as example of PPARα agent.

Melt the Gelucire® 44/14 and PEG in an adequately equipped mixer for liquid (TRIAGI, LLEAL Barcelone, Spain, or FRYMA, Basel, Switzerland) at 75°C. Add the fenofibrate powder to the molten mix. Continue the mixing while mounting the temperature of the mix to 75°C. Once fenofibrate is homogeneously dispersed in the mass, add the hydropropylcellulose at 75°C and under mixing. Finally add the disintegrating agent at 75°C and under mixing. The disintegrating agent is not dissolved in the fatty excipients but is homogeneously dispersed in the mass. Start the filling of hard gelatine or hypromellose capsules (at 70°C). Allow the capsules to cool until 30°C. At this temperature, the product becomes solid. Package adequately the capsules.

Different examples of compositions 1 to 5 are given hereinbelow:

Fenofibrate	200
Saturated polyglycolized glycerides (Gelucire 44/14)	250
Polyethyleneglycol (PEG) 8000	55
Hydropropylcellulose (HPC)	95
Sodium starch glycolate (Explotab)	20
	620 mg (composition 1)

Fenofibrate	267
Saturated polyglycolized glycerides (Gelucire 44/14)	290
Polyethyleneglycol (PEG) 8000	55
Hydropropylcellulose (HPC)	95
Polyplasdone XL (PLPXL)	20
	727 mg (composition 2)

Fenofibrate	200
Saturated polyglycolized glycerides (Gelucire 44/14)	290
Polyethyleneglycol (PEG) 10000	30
Polyethyleneglycol (PEG) 20000	30
Hydropropylcellulose (HPC)	90
Sodium starch glycolate (Explotab)	20
	660 mg (composition 3)

Fenofibrate	160
Saturated polyglycolized glycerides (Gelucire 44/14)	240
Polyethyleneglycol (PEG) 20000	48
Hydropropylcellulose (HPC)	95
Sodium starch glycolate (Explotab)	20
	563 mg (composition 4 or Fenogal ® Lidose ®)

Fenofibrate	200
Saturated polyglycolized glycerides (Gelucire 44/14)	300
Polyethyleneglycol (PEG) 20000	55
Hydropropylcellulose (HPC)	95
Croscarmellose (AC-DI-SOL)	20
	670 mg (composition 5)

Effect of the presence of an disintegrating agent

An in vitro dissolution test has been performed to assess if the presence of a disintegrating agent in the formulation allowed to increase the release and / or the dissolution of fenofibrate. As seen in figure 1, the presence of 3 %

of sodium strarch glycolate clearly increases the dissolution rate of fenofibrate.

In said figure 1, the in vitro comparative dissolution profiles of 2 semi-solid formulations of fenofibrate with and without disintegrant are shown.

The dissolution method used for said comparative study is described herebelow.

- Volume of dissolution: 900 ml
- Test temperature: 37.0 ± 0.5°C.
- Paddle rotation speed: 100 rpm.
- Test duration: 180 minutes.
- Detection : UV at 288 nm.
- Blank : dissolution medium.
- n = 6 vessels / test

The dissolution medium was 900 ml of an acidic (pH 1.2) dissolution medium containing Polysorbate 80 (2 %) as surfactant and pepsin (3.2 g/l) as enzyme.

Effect of the type of disintegrating agent

It was also interesting to assess if different disintegrating agents substances were able to increase the release and/or dissolution of fenofibrate in vitro in comparison in the same way. Therefore, the dissolution profile of a semi-solid formulation of fenofibrate containing 4% of sodium starch glycolate was compared with a semi-solid formulation of fenofibrate containing 4% of sodium croscarmellose.

Figure 2 shows the in vitro comparative dissolution profiles of 2 semi-solid fenofibrate compositions containing different disintegrating agents (dissolution method – see hereinabove).
It appears from said figure that sodium croscarmellose and sodium starch glycolate give similar increase of dissolution rate.

But an increase of the dissolution rates does not mean that the composition corresponding to the present invention allows to increase the bioavailability of fenofibrate in humans after an oral administration. Therefore, pharmacokinetic studies have been performed:

In vivo test

The bioavailability of FENOGAL® LIDOSE® 160 mg capsule (Laboratoires SMB SA) has been assessed and compared to the bioavailability of the reference (LIPIDIL-TER® 160 mg tablet, Fournier) on 18 healthy subjects. LIPIDIL-TER® 160 mg tablet is a suprabioavailable formulation of fenofibrate wherein the higher bioavailability of the drug is obtained by co-micronizing the fenofibrate together with a surfactant. LIPIDIL-TER® 160 mg is already on the market in several countries.
This study (SMB-FENO-SD012) was a single dose, two treatments, two periods, two sequences, randomised, cross-over and with at least 8 days wash-out between the two periods.
The subjects were healthy caucasian volunteers of both sexes (non-pregnant, non-breast-feeding), aged 18 to 50 years, non smokers or smoking less than 10 cigarettes per day.
The drugs (one tablet or one capsule containing 160 mg of fenofibrate in one intake during the two periods) were taken with food (a standardized breakfast).

Blood samples were collected according to the following sampling schedule : pre-dose and 1h, 2h, 3h, 4h, 5h, 6h, 7h, 9h, 12h, 24h, 36h, 48h, 60h and 72 hours post-dose.

The plasma concentrations of fenofibrate were quantified using a fully validated LC/MS/MS method.

The figure 3 describes the mean pharmacokinetic profile of fenofibrate for the two formulations (n=18 subjects).

The continuous variables (AUC_T, AUC_∞, C_{max}, $t_{1/2}$ and MRT) were evaluated according to an univariate ANOVA based on log-transformed data. For T_{max}, the non parametric Kruskal-Wallis test was used. Bioequivalence was evaluated using the Shuirman two one-sided t-test (90% CI). The Kinetica Program (Innaphase®) has been applied for this calculations.

The table hereinbelow gives the value of the main pharmacokinetics results and statistical analysis obtained for each formulation of fenofibrate.

Table 1 : Pharmacokinetic results and statistical analysis of comparative study in 18 volunteers for fenofibrate (log-transformed data)

Results			Bioequivalence tests
Parameter	LIPIDIL-TER® 160 mg	FENOGAL® LIDOSE® 160 mg	Shuirman 90% CI Range (acceptance range : 80-125)
AUC_∞ ± SD	173.29 (µg.h/ml) ± 90.82	172.43 (µg.h/ml) ± 85.78	94-105
AUC_T ± SD	161.21 (µg.h/ml) ± 74.30	160.42 (µg.h/ml) ± 70.52	94-105
C_{max} ± SD	9.54 (µg /ml) ± 1.97	9.12 (µg /ml) ± 2.10	88-103
T_{max} ± SD	4.17 (h) ± 1.38	4.50 (h) ± 0.98	/
$t_{1/2}$ ± SD	15.57 (h) ± 4.56	15.58 (h) ± 4.37	95-106
MRT ± SD	23.05 (h) ± 7.14	23.91 (h) ± 6.92	99-110

This study demonstrated that LIPIDIL-TER® 160 mg and FENOGAL® LIDOSE® 160 mg are bioequivalent after a single oral dose administration of each product in fed conditions. Indeed, the pharmacokinetics parameters AUC (AUC_∞ and AUC_T), C_{max} , T_{max} , $t_{1/2}$ and MRT were within the predetermined confidence interval. Consequently, the present invention

allows to obtain a similar suprabioavailable product as LIPIDIL-TER® 160 mg but with a very simplier and cheaper manufacturing process.

Compositions similar to compositions 1 to 5 have been prepared by replacing the fenofibrate powder by the following PPAR agents :

- bezafibrate;
- ciprofibrate,
- Clofibrate,
- Gemfibrozil,
- Bezafibrate (10-90%) + fenofibrate (90-10%)

CLAIMS

1. An oral semi-solid or liquid composition for treating hyperlipidemia or hypercholesterolemia in humans, which comprises at least an effective amount of a peroxisome proliferator activated receptor alpha agent (PPARα), one polyglycolized glyceride and one hydrophilic disintegrating agent.
2. The composition of claim 1, wherein the PPARα agent is fenofibrate.
3. The composition of claim 1 wherein the PPARα is bezafibrate, ciprofibrate.
4. The composition of claim 1, wherein the disintegrating agent is sodium starch glycolate.
5. The composition of claim 1, wherein the disintegrating agent is sodium croscarmellose, crospovidone, starch, colloidal silicone dioxide or another pharmaceutically accepted disintegrating agent.
6. The composition of claim 1 further containing a polyethylene glycol or a mix of polyethylene glycol with different molecular mass.
7. The composition of claim 1, wherein a suspension stabilizer is added in the composition.
8. The composition of claim 7, wherein the suspension stabilizer is a cellulose derivative.
9. The composition of claim 8, wherein the suspension stabilizer is hydropropylcellulose.
10. The composition of claim 2, wherein said fenofibrate is present in amount of 10% to 80% per weight based on the total weight of the formulation.
11. The composition of claim 2, wherein the amount of fenofibrate per dose is between 30 and 400 mg.

12. The composition of claim 1, wherein the composition is filled in hard gelatine capsules, hypromellose capsules or in other pharmaceutically acceptable capsules.
13. The composition of claim 2, which is with the proviso that the fenofibrate is not co-micronized.
14. The composition of claim 1, in which the weight ratio PPAR agent/hydrophilic disintegrating agent is comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, more preferably between 6 and 25, while the weight ratio PPAR agent/polyglycolized glyceride(s) is comprised between 10 and 0.1, advantageously between 5 and 0.5, preferably greater than 1, more preferably between 1.1 and 2.
15. A method for treating or preventing hyperlipidemia or hypercholesterolemia in a patient, in which at least an effective amount of a peroxisome proliferator activated receptor agent is orally administered to the patient simultaneously with at least one polyglycolized glyceride and one hydrophilic disintegrating agent.
16. A process for the preparation of an oral semi-solid or liquid composition containing at least an effective amount of PPAR agent, at least one polyglycolised glyceride and one hydrophilic disintegrating agent, in which the PPAR agent in powder form and hydrophilic disintegrating agent are mixed to a molten mixture containing at least one polyglycolisedz glyceride.
17. The process of claim 16, in which the PPAR agent and the hydrophilic disintegrating agent are mixed successively with the molten mixture.
18. The process of claim 17, in which the PPAR agent is first mixed with the molten mixture, and in which before adding the hydrophilic disintegrating agent, the homogeneous dispersion of the PPAR powder in the molten mixture is controlled.

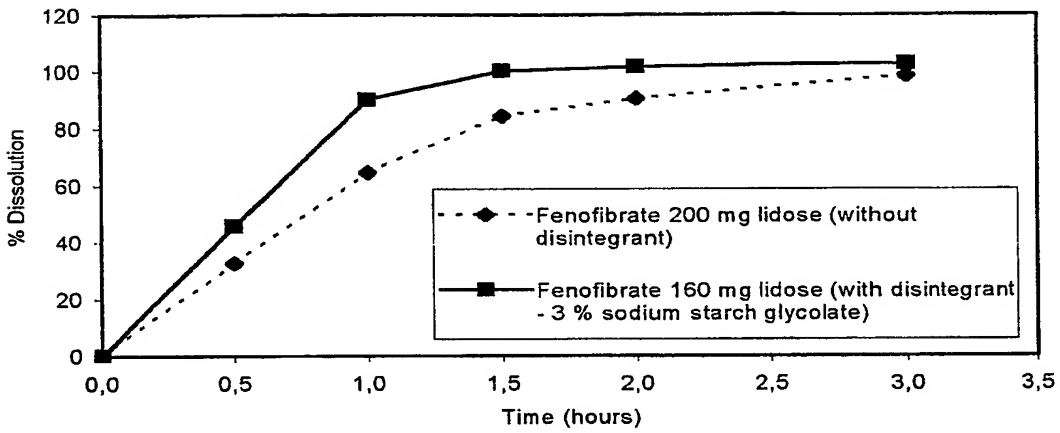

Figure 1

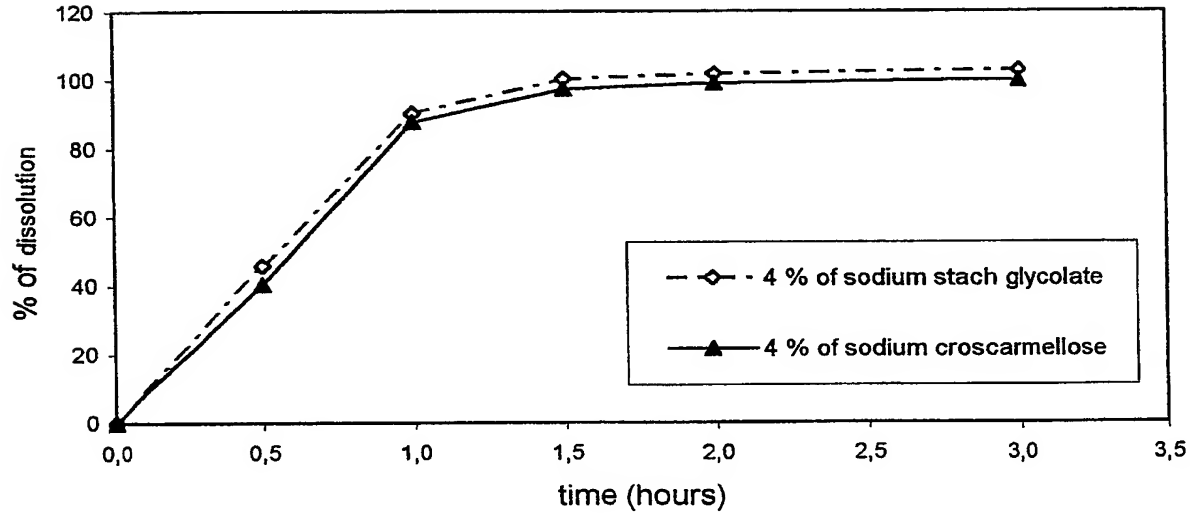

Figure 2

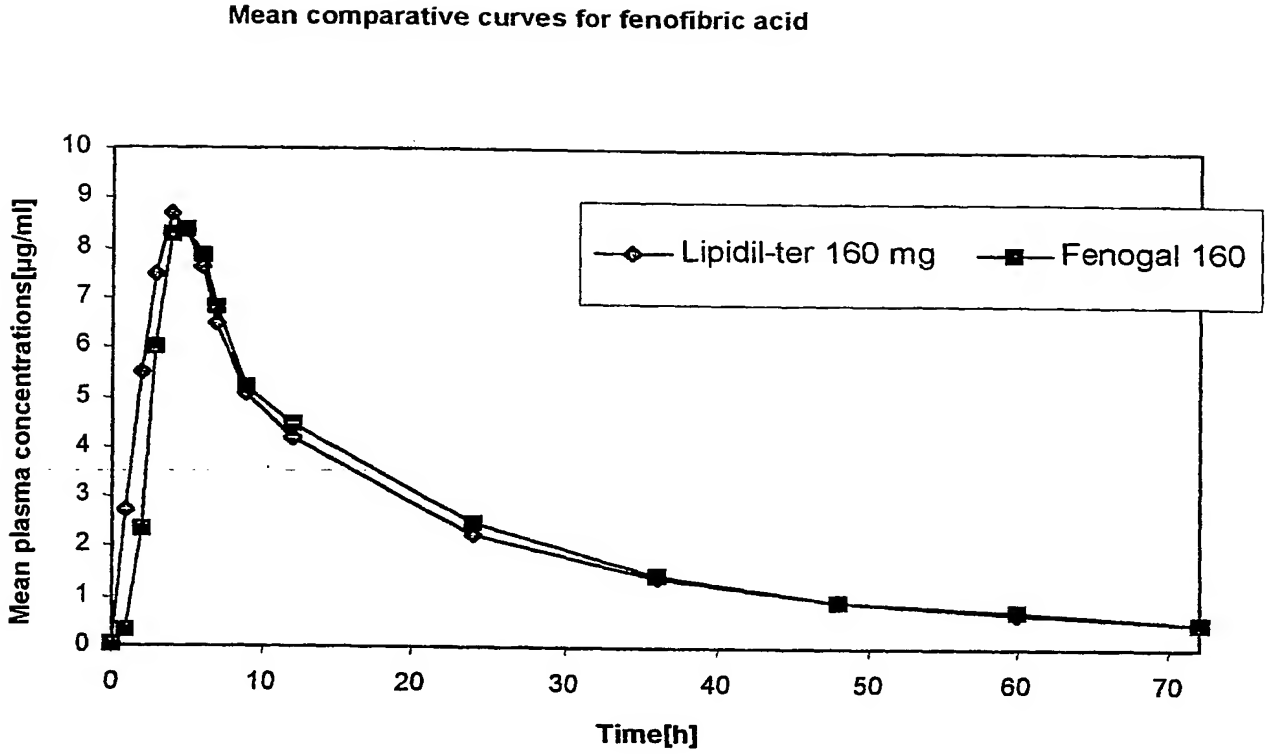
Mean comparative curves for fenofibric acid
Mean plasma concentrations[µg/ml]
Time[h]
Lipidil-ter 160 mg
Fenogal 160
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60
70

Figure 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 02/00051

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/215 A61K9/48 A61K31/00 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 12528 A (SMB TECHNOLOGY) 18 March 1999 (1999-03-18) claims 1,9,10,12,14,16 page 7, line 17 -page 8, line 5 page 8, line 23 -page 9, line 7 page 9, line 26 -page 10, line 11 ---	1,2, 5-13, 16-18
X	WO 01 21154 A (RTP PHARMA) 29 March 2001 (2001-03-29) claims 1,3,9-11 page 16, paragraph 4 -page 17 page 28 --- -/--	1,2, 5-13, 16-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2002	06/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 02/00051

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 59475 A (LIPOCINE) 12 October 2000 (2000-10-12) claims 1,4,21-24,48-50,53,69,74 page 27 page 45, line 28 -page 46, line 12 page 47, line 18-30 page 53, line 1-7	1-3,5-8, 12,13, 16-18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/BE 02/00051

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 1,4-9,12,14-18 relate to a product/compound/method defined by reference to a desirable characteristic or property, namely: Peroxisome proliferator activated receptor alpha agent (PPAR-alpha).

The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely claims 2,3,10,11,13 and for the examples with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

ational Application No
rCT/BE 02/00051

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9912528 A	18-03-1999	BE 1011363 A3	03-08-1999
		WO 9912528 A1	18-03-1999
WO 0121154 A	29-03-2001	AU 7984200 A	24-04-2001
		EP 1214059 A2	19-06-2002
		WO 0121154 A2	29-03-2001
WO 0059475 A	12-10-2000	US 6383471 B1	07-05-2002
		AU 3763700 A	23-10-2000
		EP 1165048 A1	02-01-2002
		WO 0059475 A1	12-10-2000